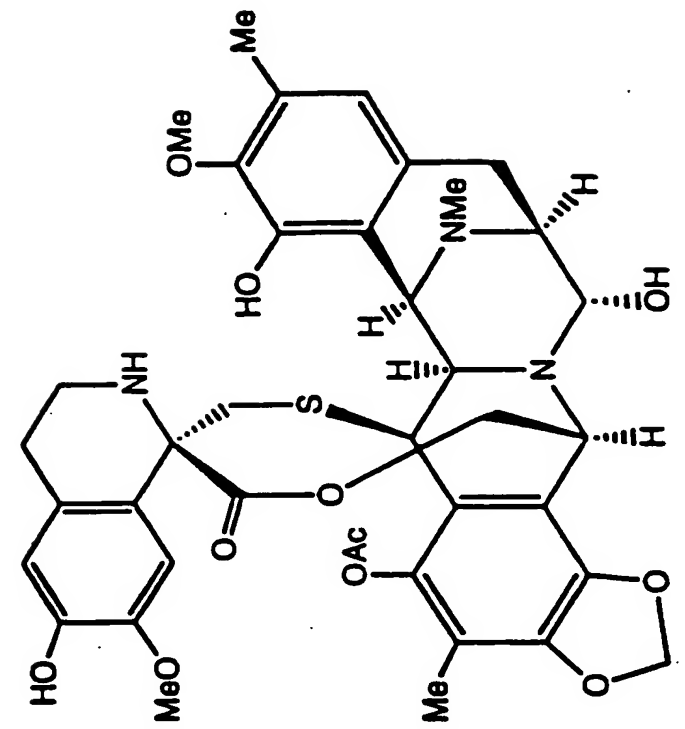

Me
OMe
HO
NMe
H
OH
H
N
NH
S
H
O
O
OAc
HO
MeO
Me
O
O

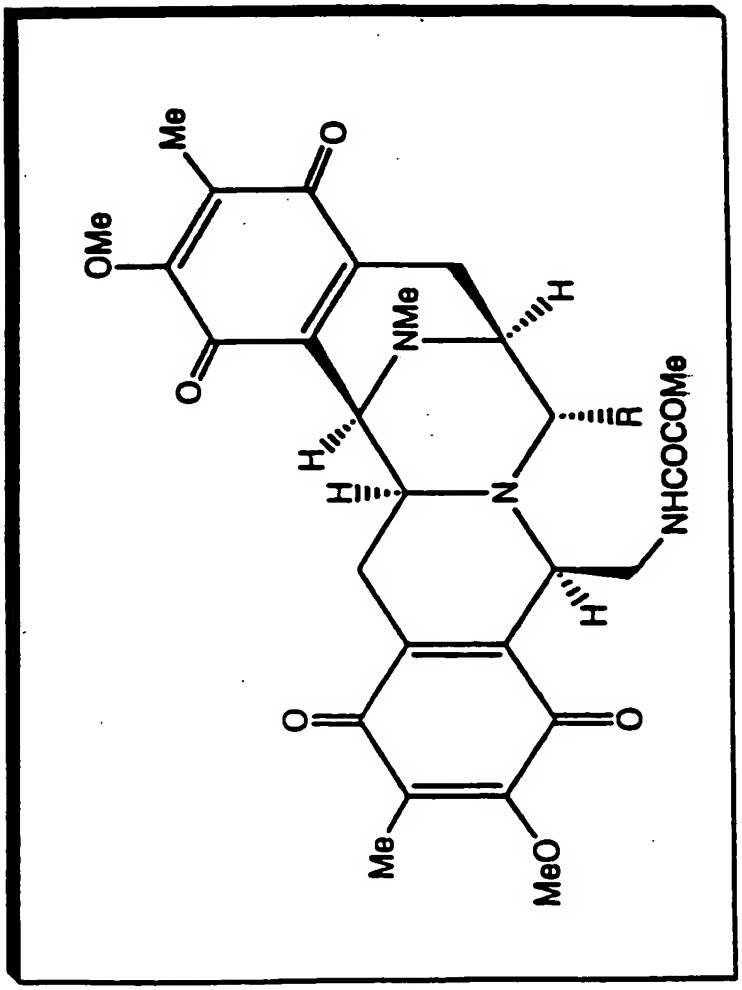
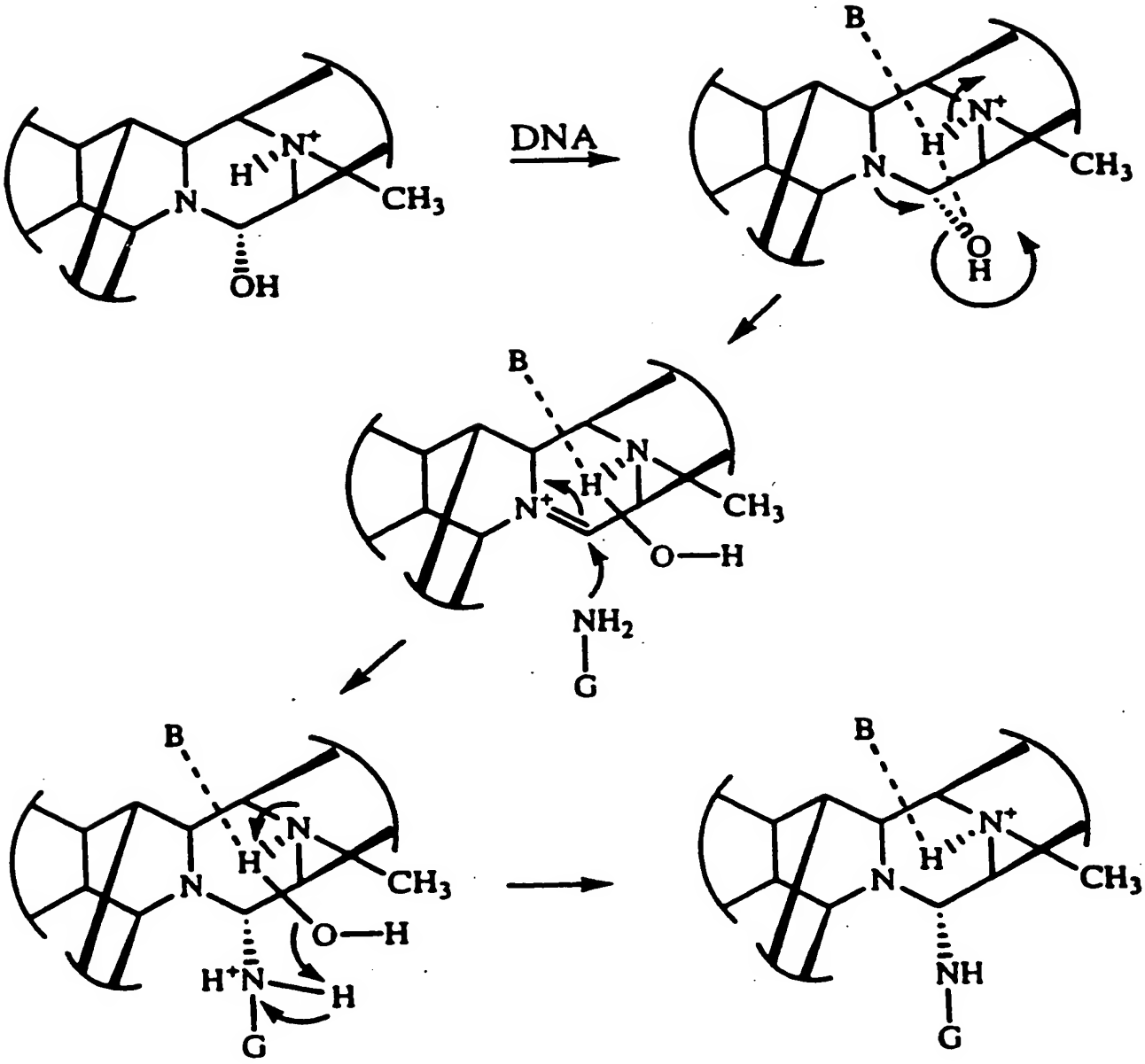

Me
O
OMe
NMe
H
O
R
H
H
N
NHCOCOMe
H
O
O
Me
MeO

FIGURE 1

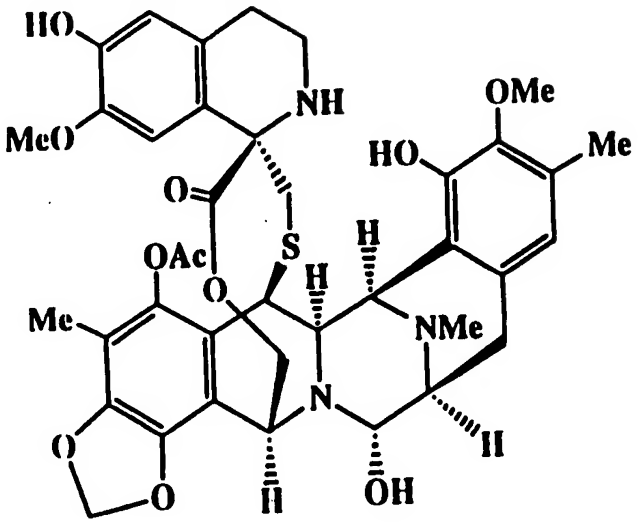
# FIGURE 2

| Cell lines, $IC_{50}$ (ng/mL) | | Synthesis inhibition $IC_{50}$ (μg/mL) | |
|---|---|---|---|
| P 388 | 0.2 | Prot | >1 |
| A 549 | 0.2 | | |
| HT 29 | 0.5 | DNA | 0.1 |
| MEL 28 | 5.0 | RNA | 0.03 |
| CV-1 | 1.0 | | |

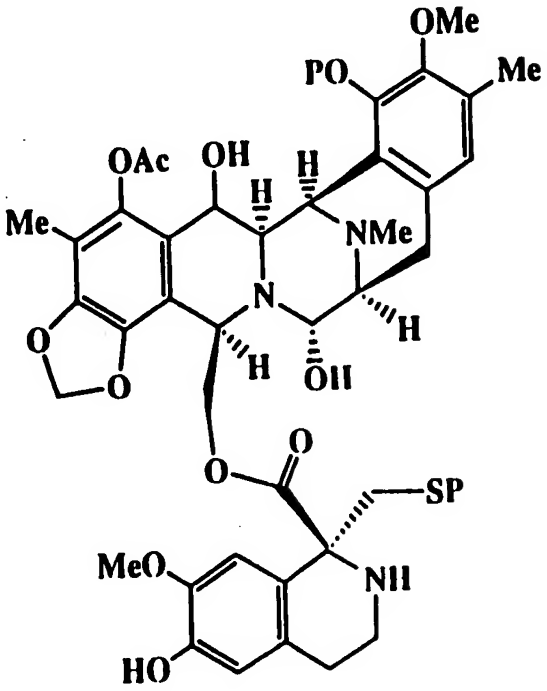
# FIGURE 3

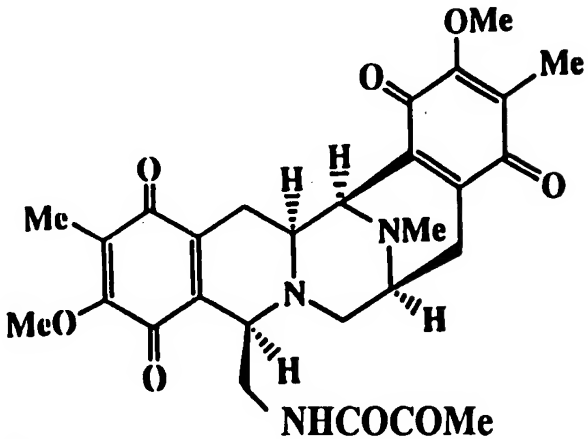


# FIGURE 4A

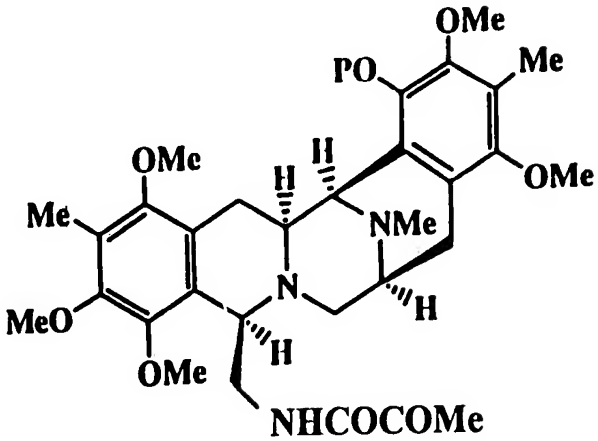



ET 743

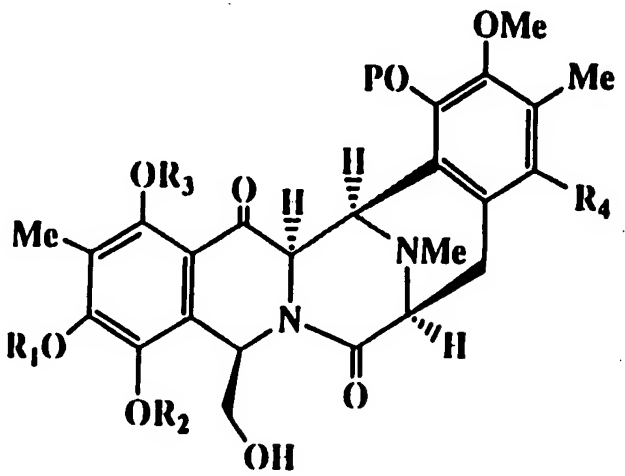



Saframycin B

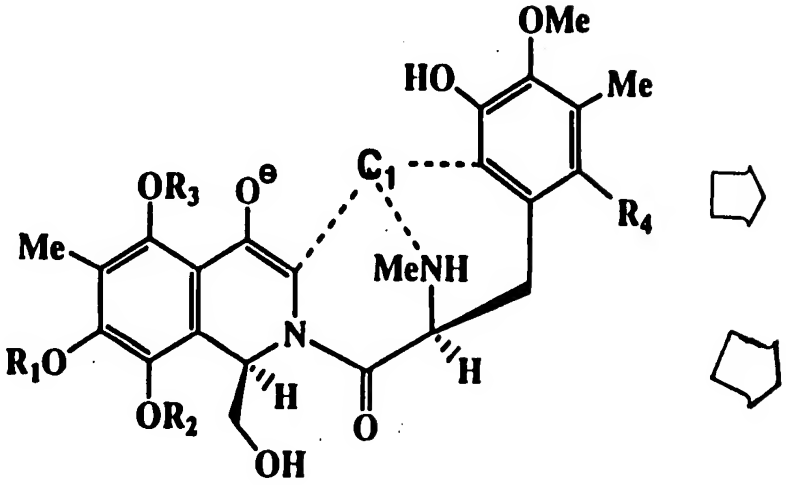


# FIGURE 4B

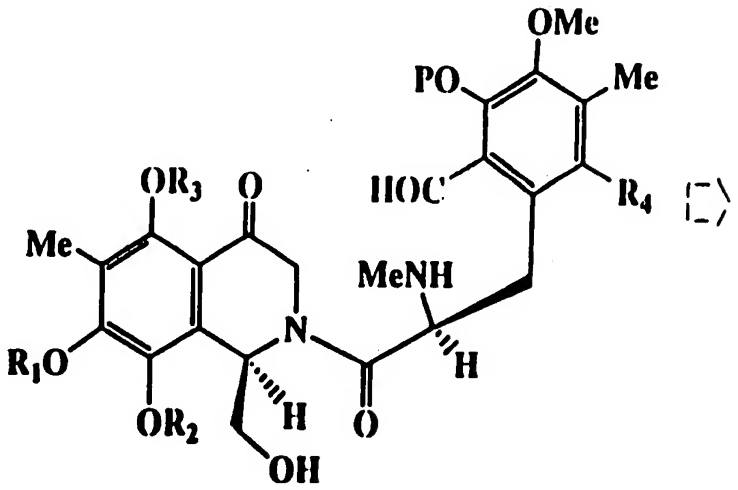



A

B




**Strategy A: $C_1$ insertion, one carbon equivalent, *i.e.*: $(RO)_3CH$, $MeOCH(NMe_2)_2$**



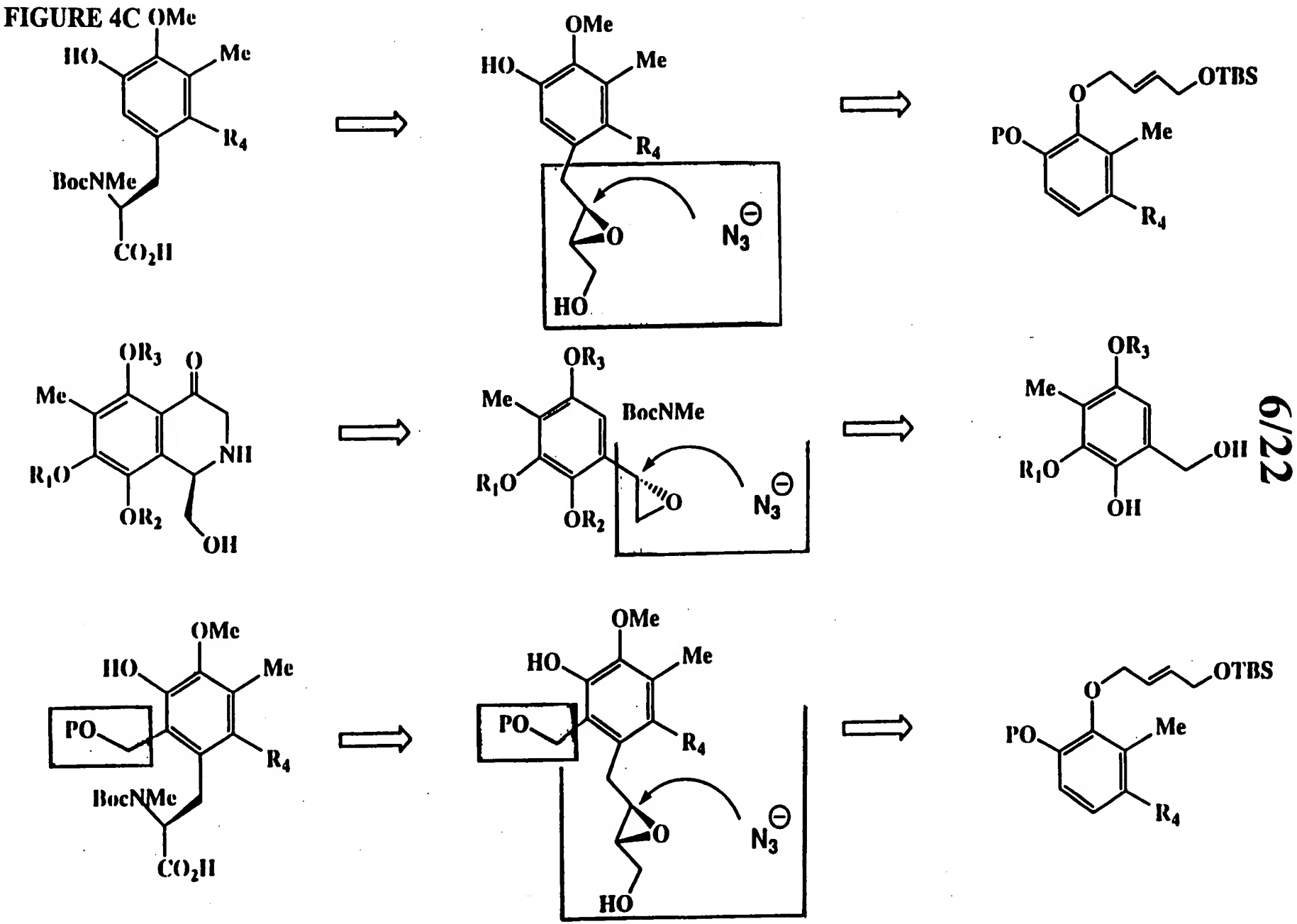

**Strategy B: Mannich-like cyclization**

**Intermediate for :**

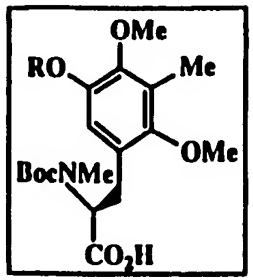
**Safracin B: $R_1=R_2=R_3=Me$, $R_4=OMe$**

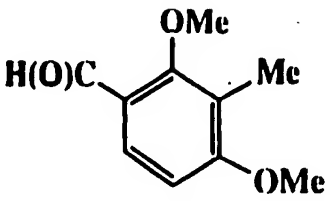
**ET 743: $R_1$, $R_2=-CH_2-$, $R_3=Ac$, $R_4=H$**

FIGURE 4C



# FIGURE 5A

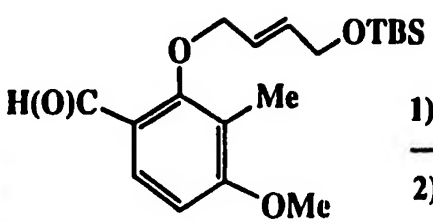



1) $BCl_3$, $CH_2Cl_2$, 0°C
2) 

$K_2CO_3$, $CH_3CN$, 80°C

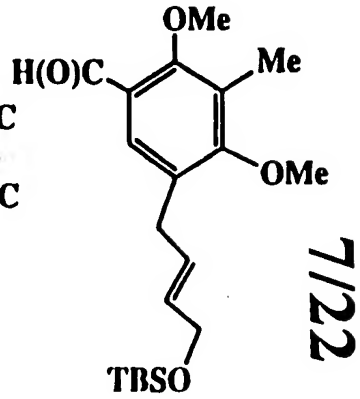
> 95%




1) $Me_2NPh$, Toluene, 210°C

2) MeI, $K_2CO_3$, DMF, 80°C

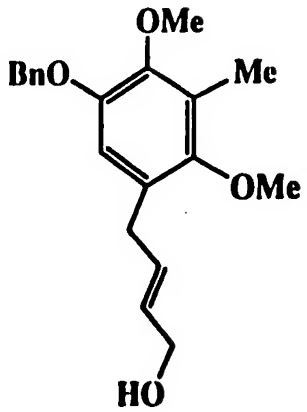
> 70%




1) $SeO_2$, $H_2O_2$, t-BuOH, 40°C
then $Et_3N$, MeOH

2) BnBr, $K_2CO_3$, $CH_3CN$, 80°C
3) TBAF, THF

> 70%

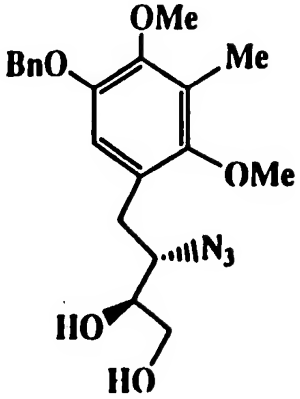



1) SAE, (D)DET, $Ti(iOPr)_4$, tBuOOH,
4Åm.s., $CH_2Cl_2$, 98% (>95%ee)

2) $Ti(OiPr)_2(N_3)_2$, PhH, reflux

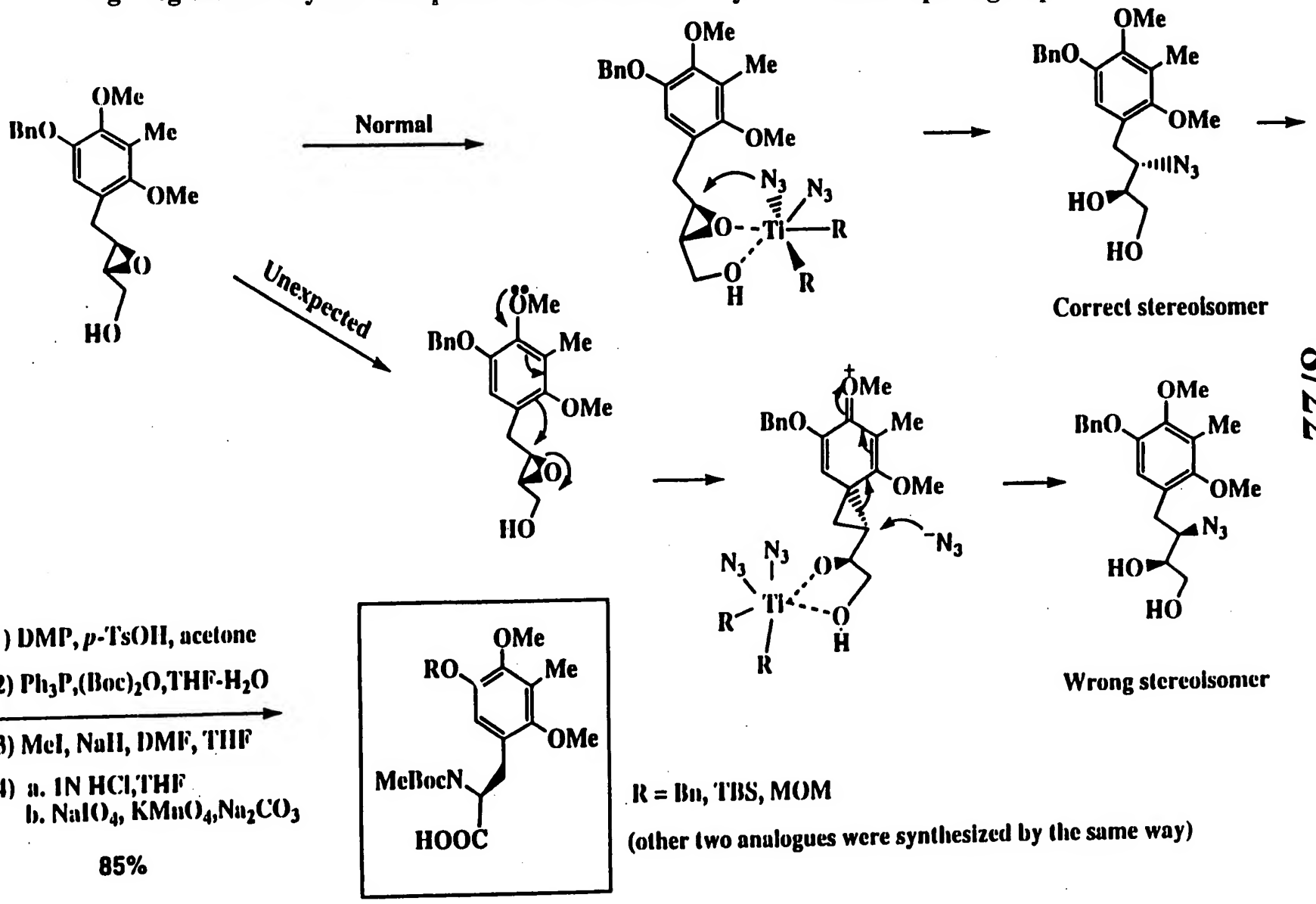
regio-selectivity > 13:1
stereo-selectivity > 3:1

50%

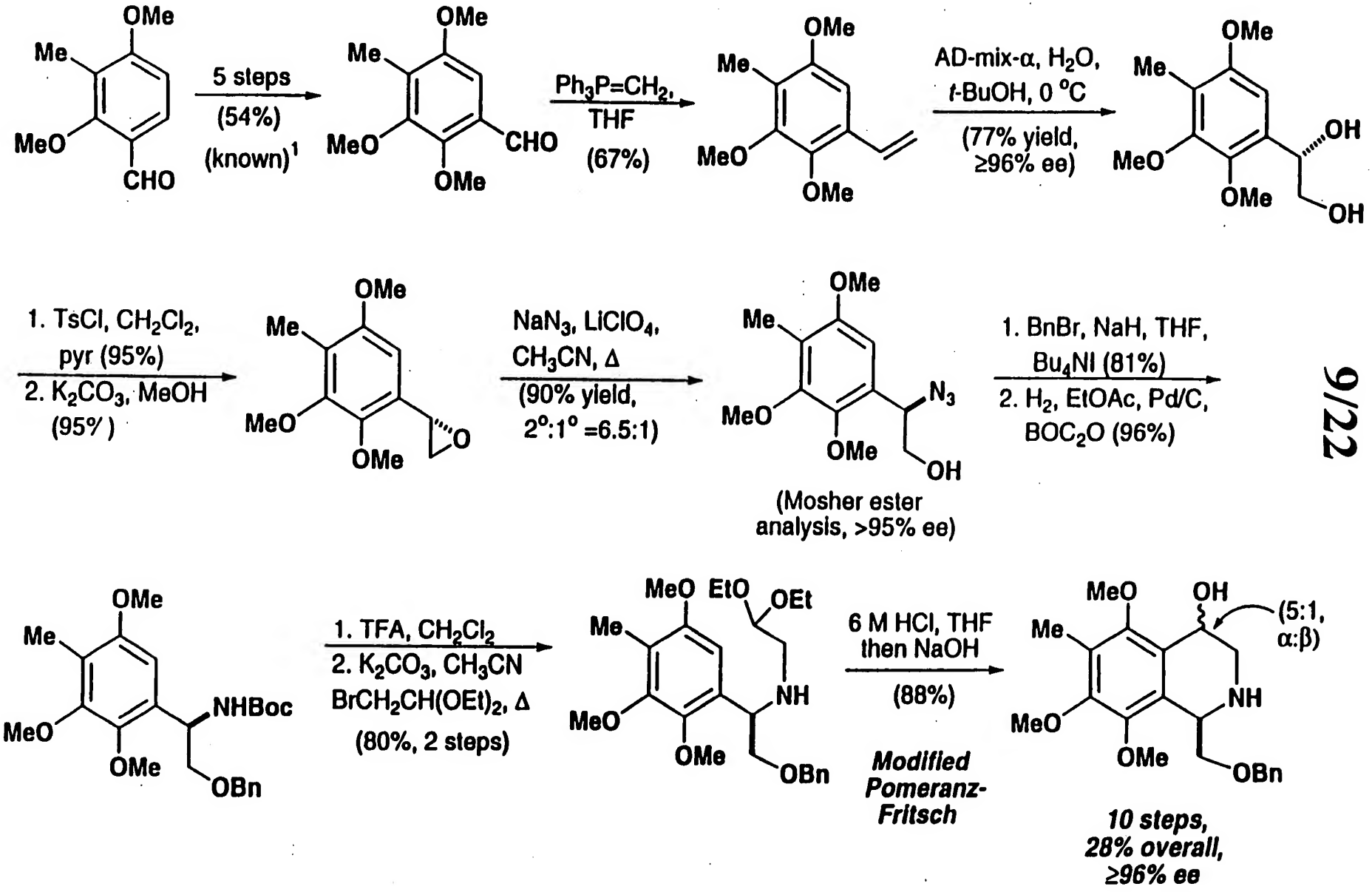


# FIGURE 5B

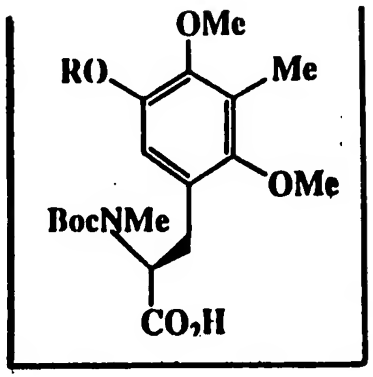
**High regioselectivity and unexpected low stereoselectivity for the azide-opening step:**



# FIGURE 6


OMe
Me
MeO
CHO
5 steps
(54%)
(known)[1]
CHO
Ph3P=CH2,
THF
(67%)
AD-mix-α, H2O,
t-BuOH, 0 °C
(77% yield,
≥96% ee)
OH
OH
1. TsCl, CH2Cl2,
pyr (95%)
2. K2CO3, MeOH
(95%)
NaN3, LiClO4,
CH3CN, Δ
(90% yield,
2°:1° =6.5:1)
N3
1. BnBr, NaH, THF,
Bu4NI (81%)
2. H2, EtOAc, Pd/C,
BOC2O (96%)
(Mosher ester
analysis, >95% ee)
NHBoc
OBn
1. TFA, CH2Cl2
2. K2CO3, CH3CN
BrCH2CH(OEt)2, Δ
(80%, 2 steps)
MeO EtO
OEt
NH
6 M HCl, THF
then NaOH
(88%)
Modified
Pomeranz-
Fritsch
(5:1,
α:β)
10 steps,
28% overall,
≥96% ee

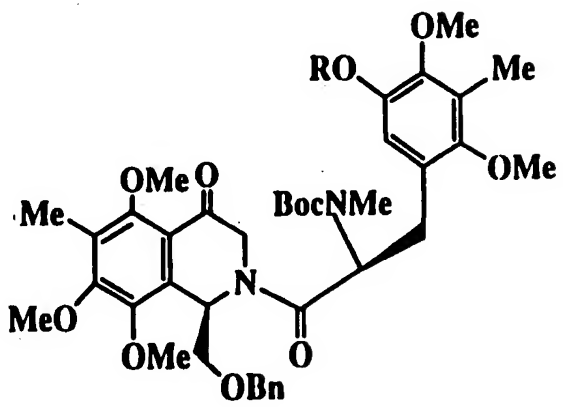
# FIGURE 7A




1) BOPCl, $Et_3N$, $CH_2Cl_2$

2) Dess-Martin P., $CH_2Cl_2$

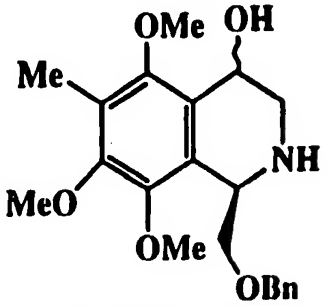
60%



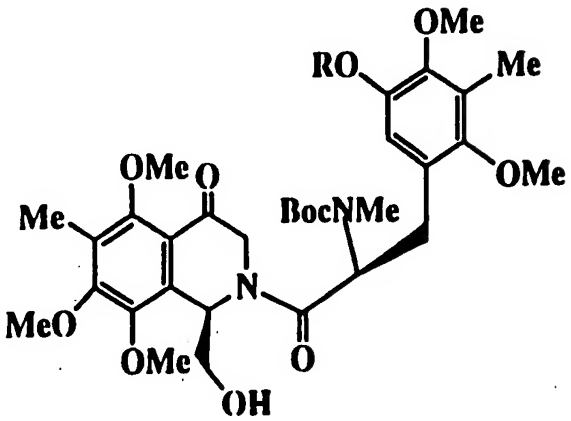

R = Bn, TBS, MOM

$H_2$, Pd/C, EtOAc

or TBAF, THF

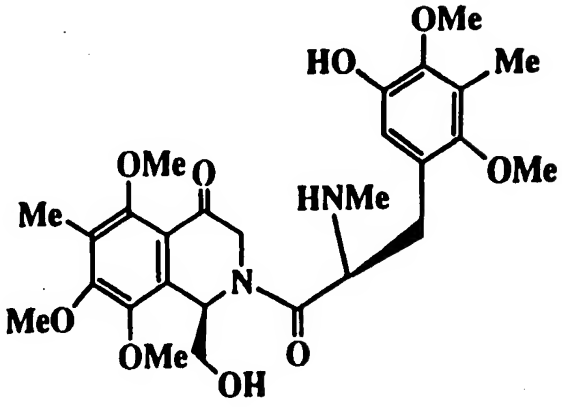



4:1 diastereomers

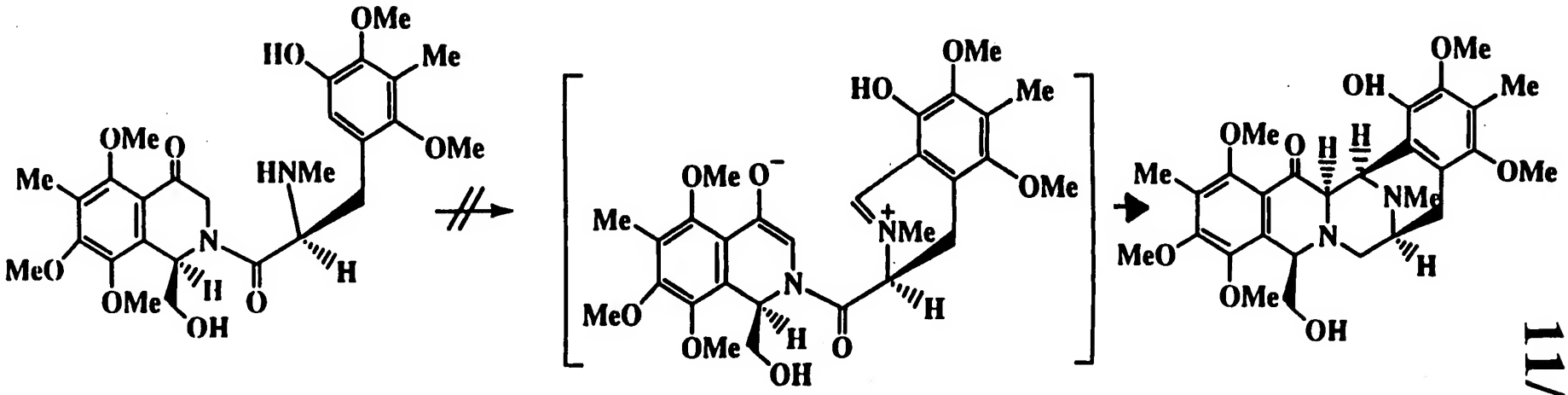



R = H, MOM

$TFA\text{-}CH_2Cl_2$

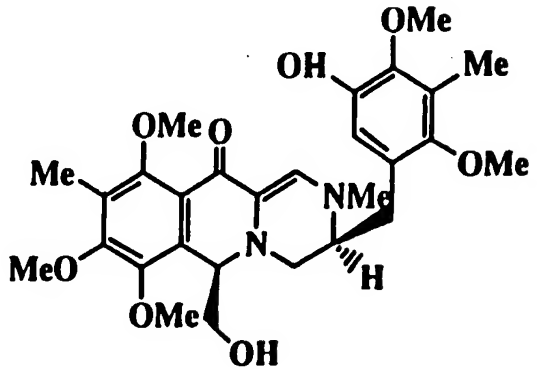


# FIGURE 7B



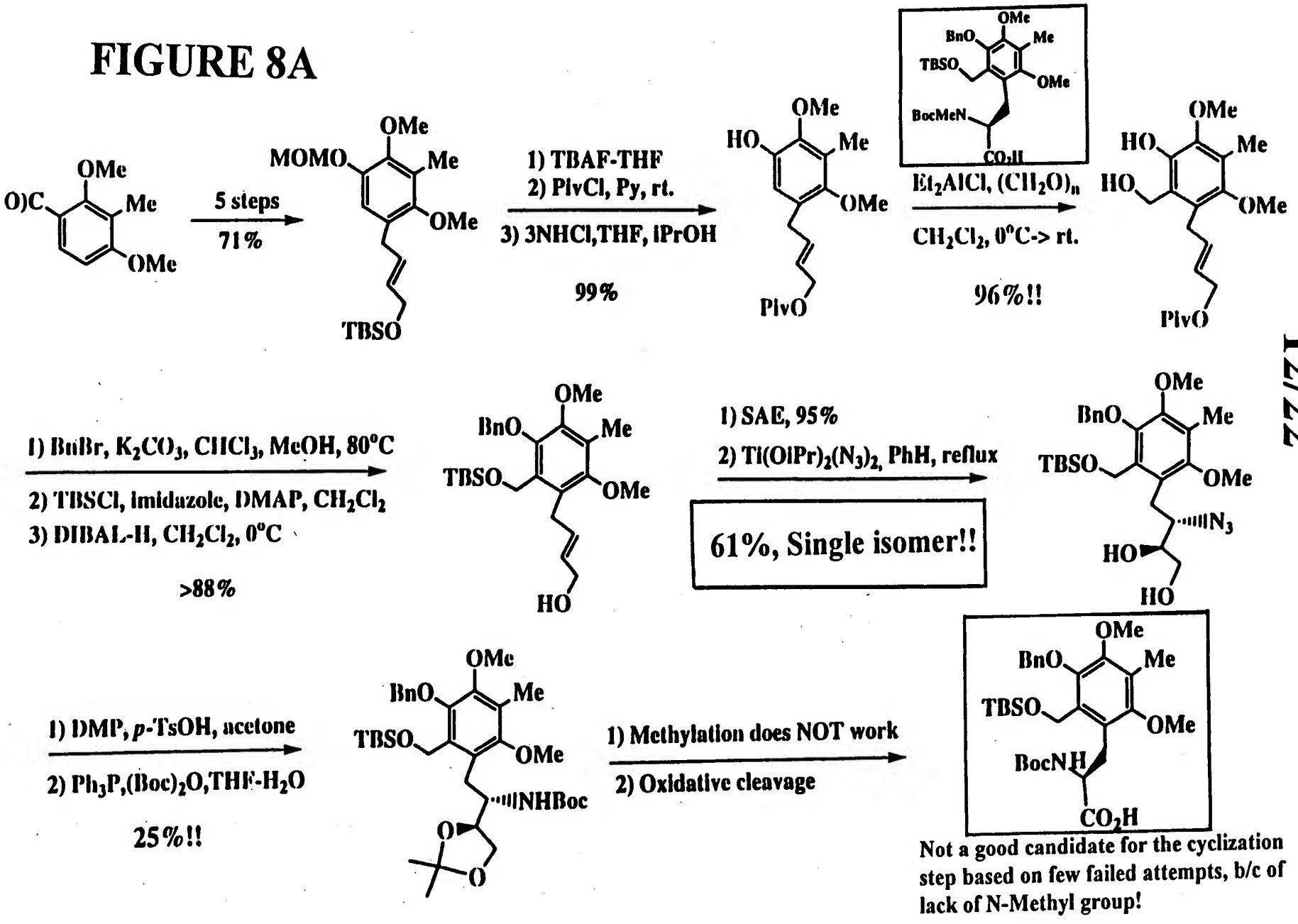



| Cyclization Conditions: | Product: |
|---|---|
| > $CH(OMe)_3$, $BF_3{\cdot}Et_2O$, reflux | - |
| > $CH(OMe)_3$, HCl or $CH_3SO_3H$, r.t. or heat | - |
| > $Cl_2CHOCH_3$, $TiCl_4$, $CH_2Cl_2$, 0°C-> reflux | - |
| > Acetic formyl anhydride, $CH_2Cl_2$, $POCl_3$, DMF | - |
| > $CH(OMe)_3$, polyphosphoric acid, reflux | - |
| > *t*-BuOCH$(NMe_2)_2$, toluene, r.t. or reflux | compound A |



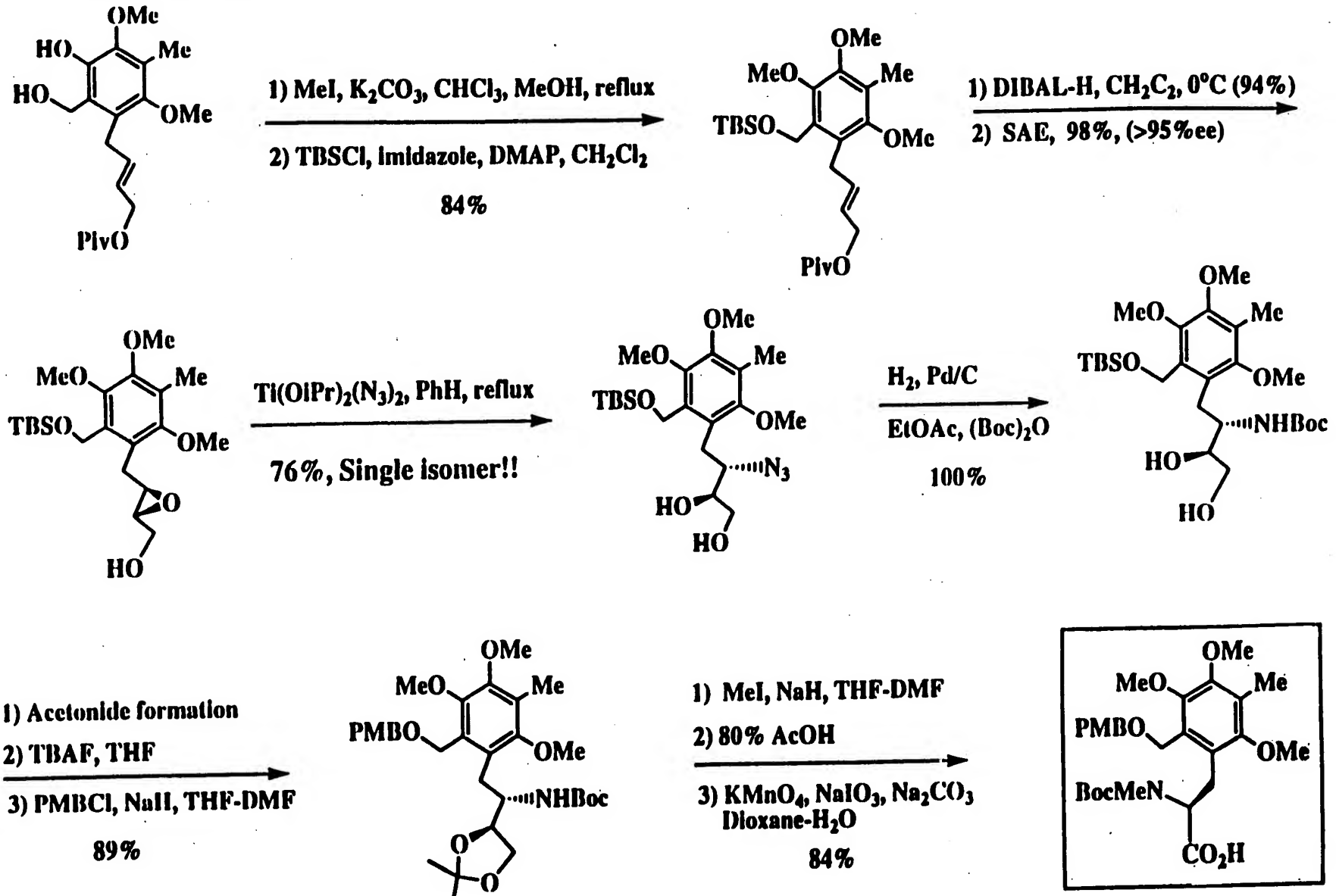

Compound A

# FIGURE 8A

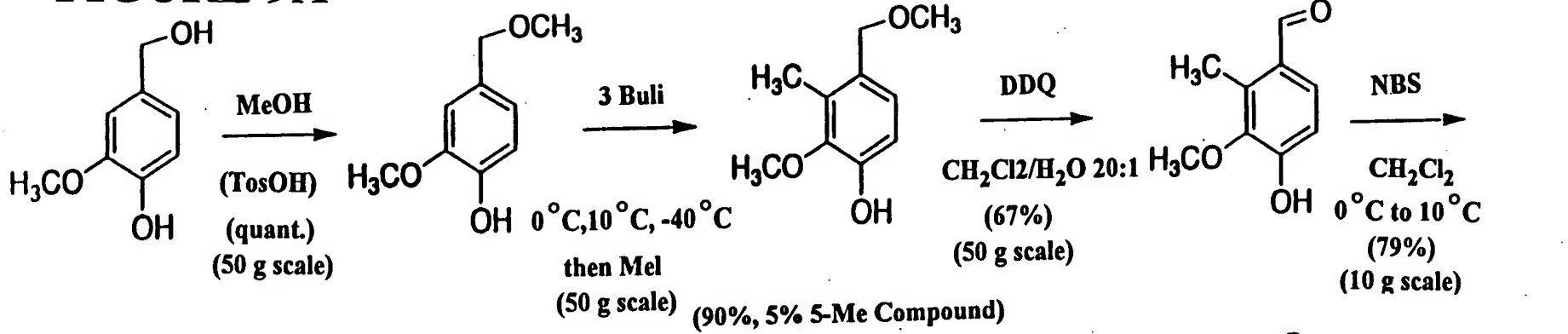



Not a good candidate for the cyclization step based on few failed attempts, b/c of lack of N-Methyl group!

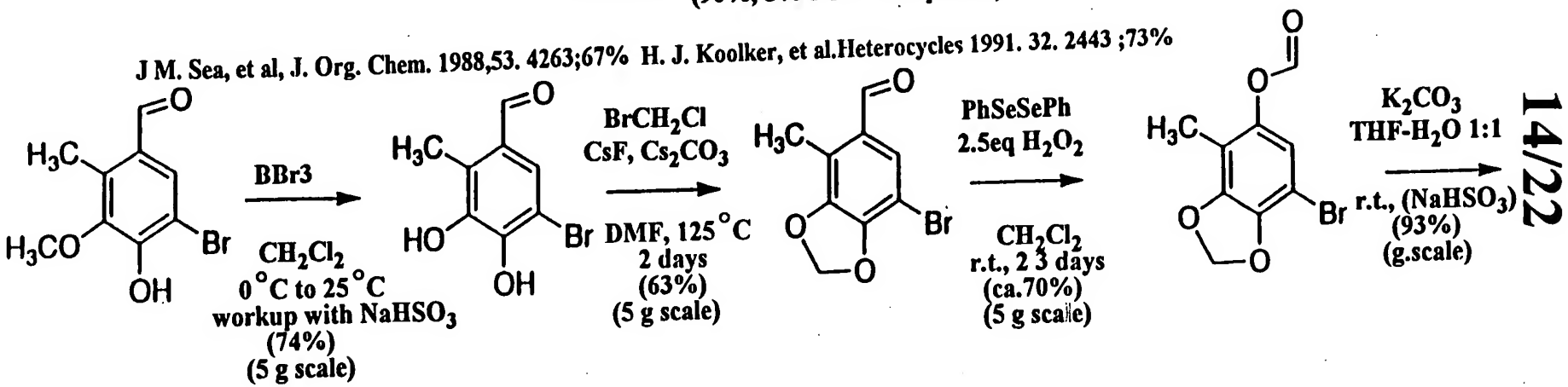
# FIGURE 8B

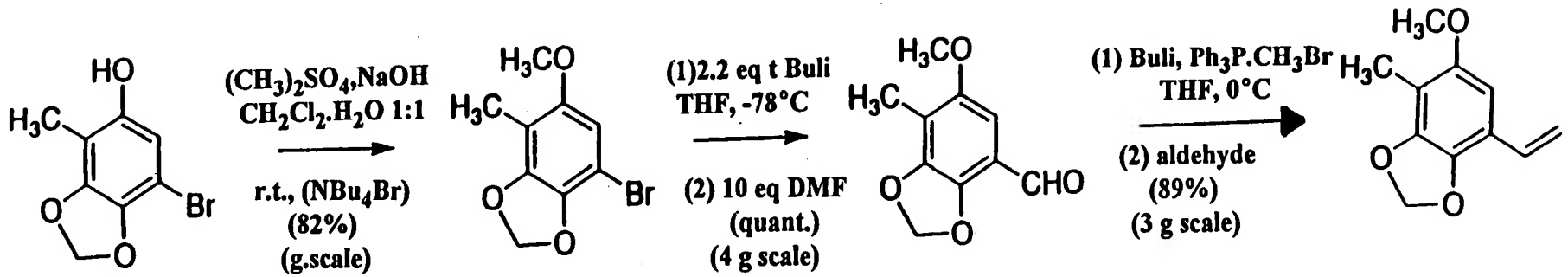

1) MeI, $K_2CO_3$, $CHCl_3$, MeOH, reflux
2) TBSCl, Imidazole, DMAP, $CH_2Cl_2$
84%
1) DIBAL-H, $CH_2C_2$, 0°C (94%)
2) SAE, 98%, (>95%ee)
$Ti(OiPr)_2(N_3)_2$, PhH, reflux
76%, Single isomer!!
$H_2$, Pd/C
EtOAc, $(Boc)_2O$
100%
1) Acetonide formation
2) TBAF, THF
3) PMBCl, NaH, THF-DMF
89%
1) MeI, NaH, THF-DMF
2) 80% AcOH
3) $KMnO_4$, $NaIO_3$, $Na_2CO_3$
Dioxane-$H_2O$
84%

# FIGURE 9A

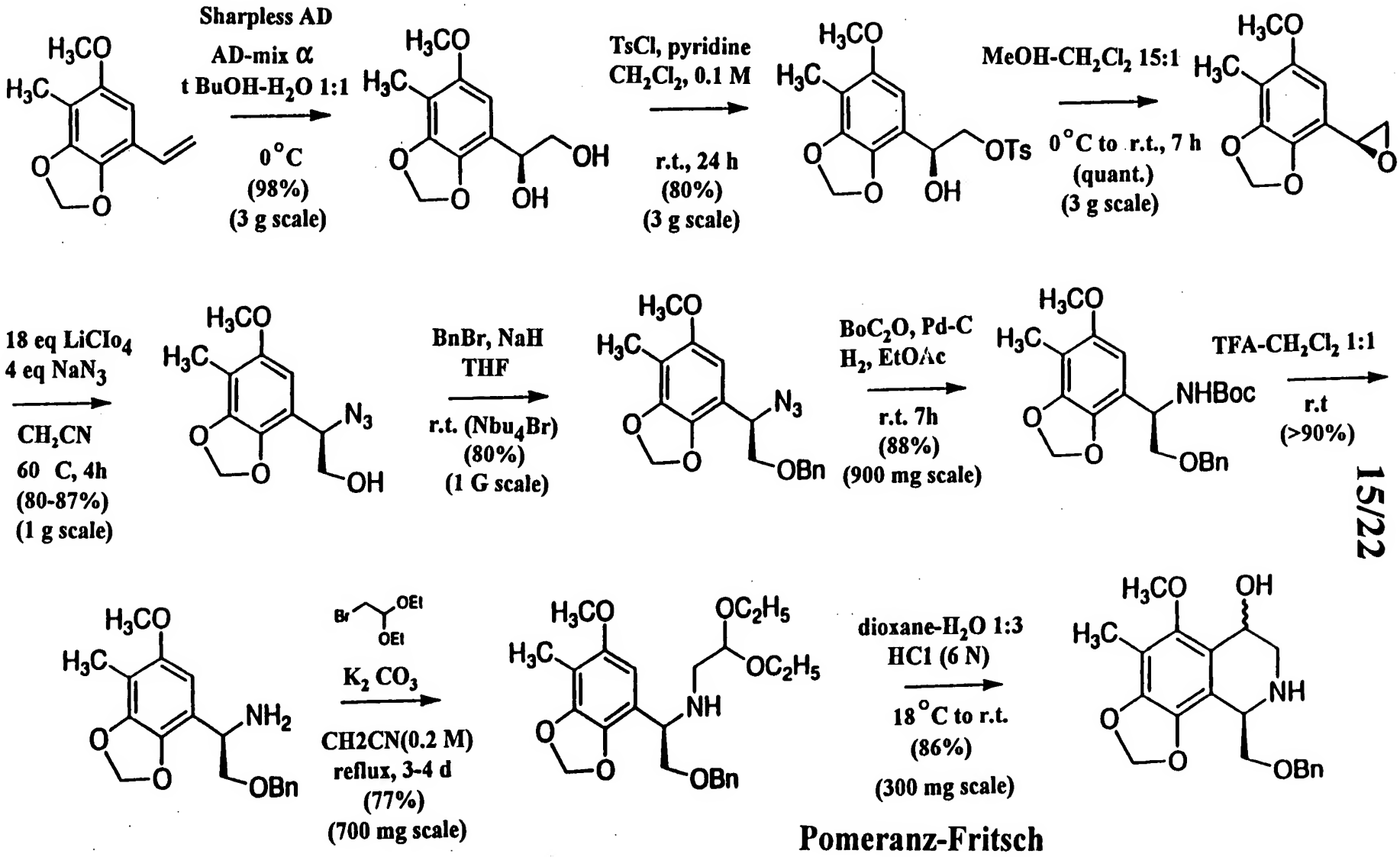



J M. Sea, et al, J. Org. Chem. 1988,53. 4263;67% H. J. Koolker, et al.Heterocycles 1991. 32. 2443 ;73%

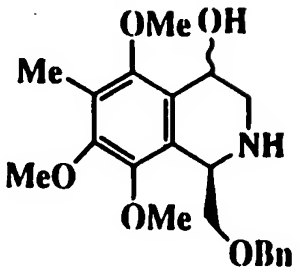


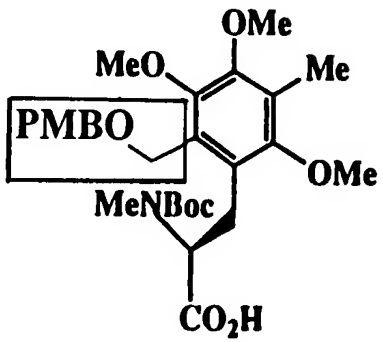
# FIGURE 9B


Sharpless AD
AD-mix α
t BuOH-H2O 1:1
0°C
(98%)
(3 g scale)
TsCl, pyridine
CH2Cl2, 0.1 M
r.t., 24 h
(80%)
(3 g scale)
MeOH-CH2Cl2 15:1
0°C to r.t., 7 h
(quant.)
(3 g scale)
18 eq LiClO4
4 eq NaN3
CH2CN
60 C, 4h
(80-87%)
(1 g scale)
BnBr, NaH
THF
r.t. (Nbu4Br)
(80%)
(1 G scale)
BoC2O, Pd-C
H2, EtOAc
r.t. 7h
(88%)
(900 mg scale)
TFA-CH2Cl2 1:1
r.t
(>90%)
K2 CO3
CH2CN(0.2 M)
reflux, 3-4 d
(77%)
(700 mg scale)
dioxane-H2O 1:3
HCl (6 N)
18°C to r.t.
(86%)
(300 mg scale)
Pomeranz-Fritsch

# FIGURE 10A



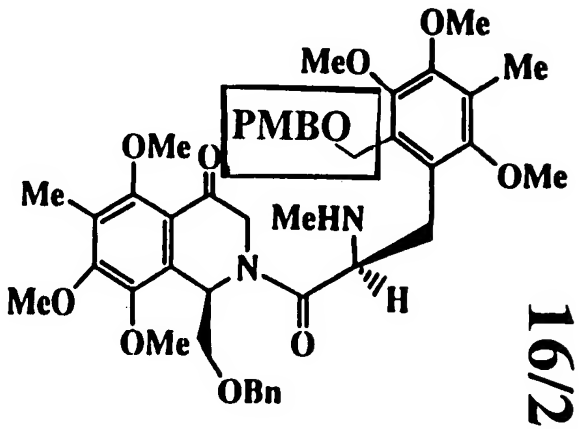

4:1 diastereomers




1) BOPCl, $Et_3N$, $CH_2Cl_2$

2) Dess-Martin Oxidation

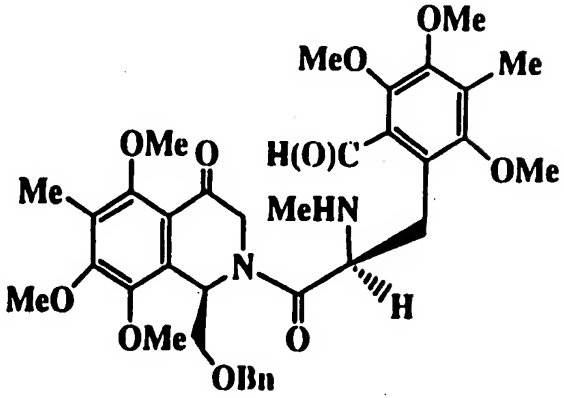
-50%




1) DDQ, $CH_2Cl_2$, $H_2O$

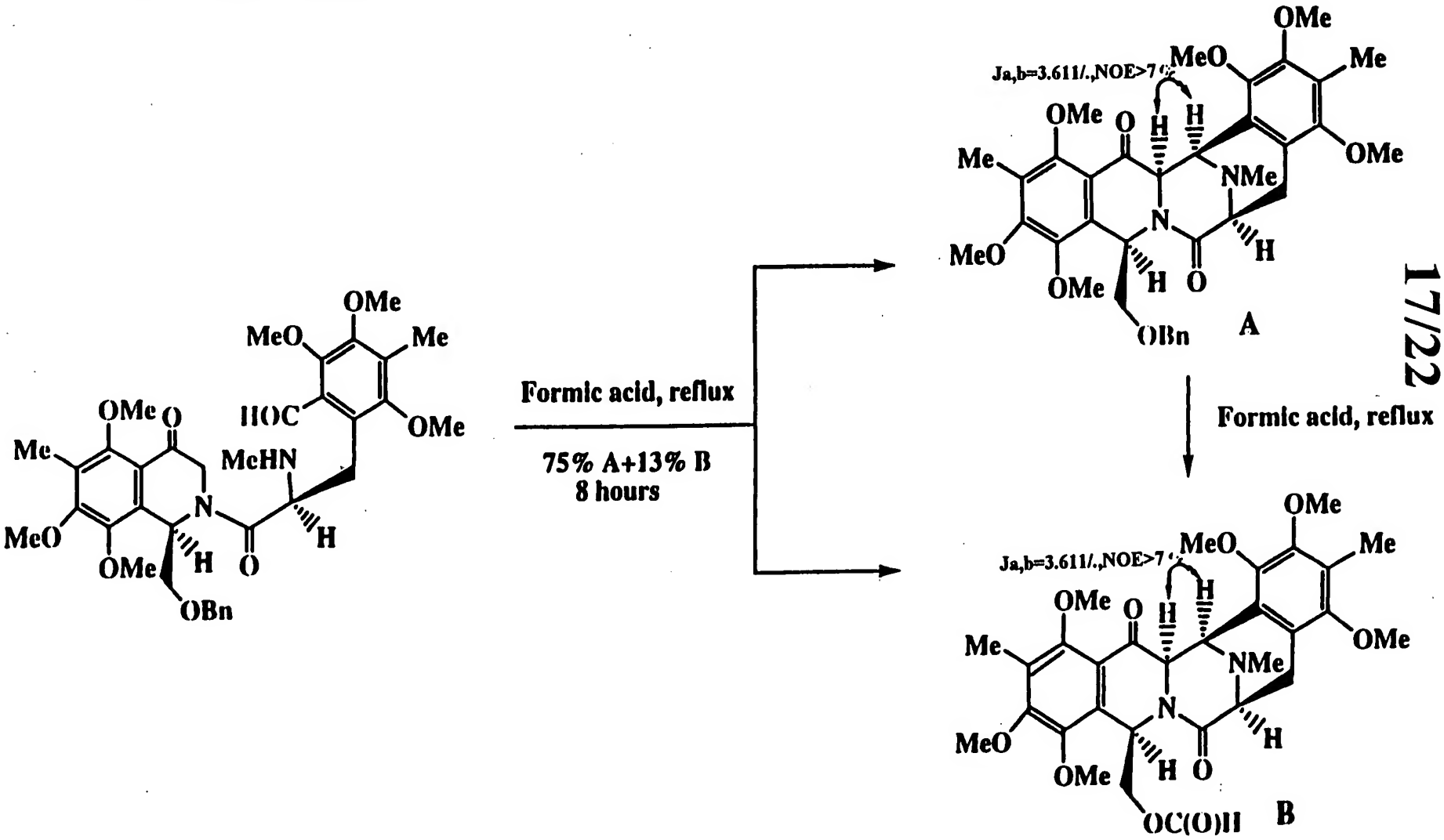
2) NMO, TPAP, 4 Å m.s., $CH_2Cl_2$

-70%

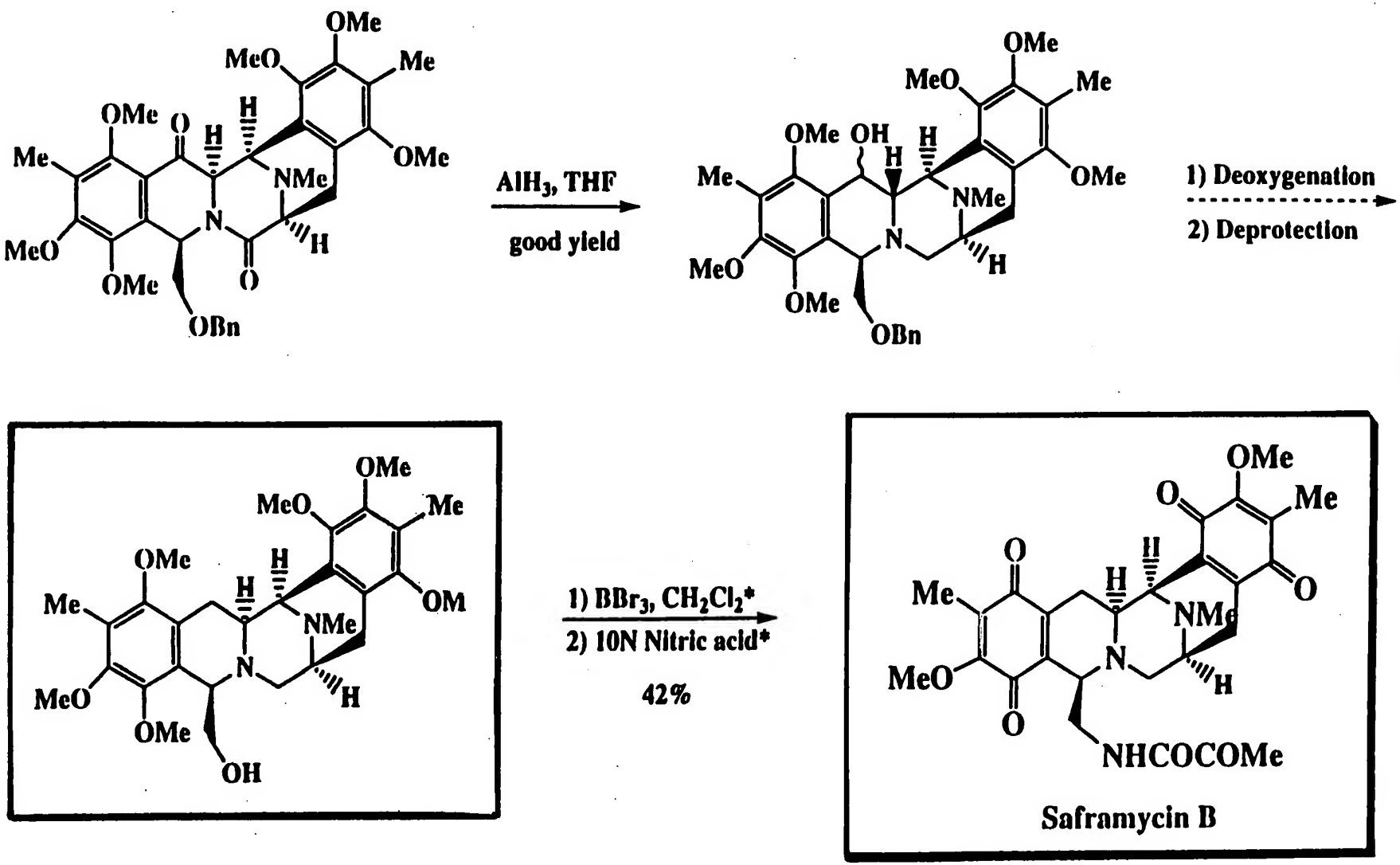



Homochiral product !

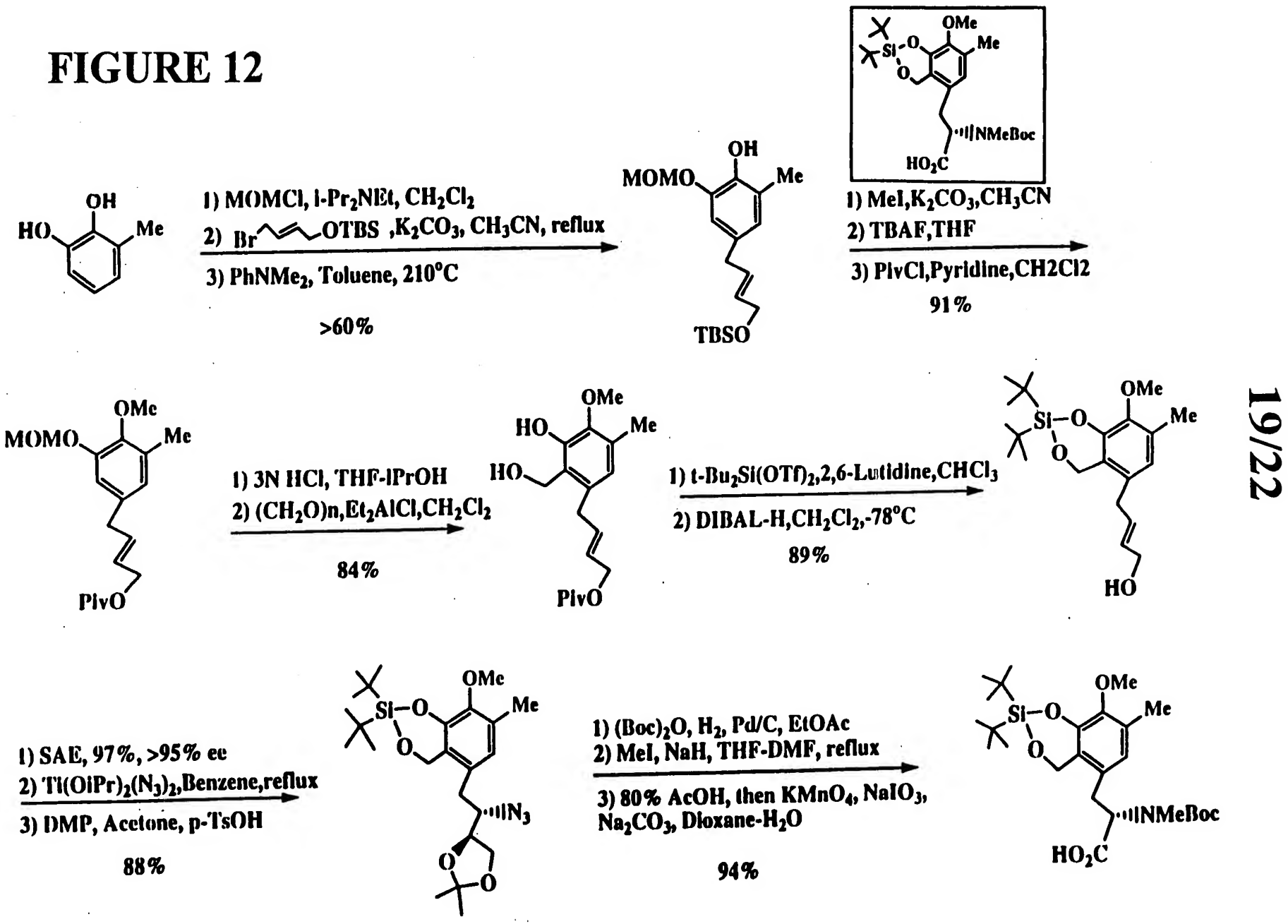
# FIGURE 10B


Formic acid, reflux
75% A+13% B
8 hours
Ja,b=3.611/.,NOE>7%
A
Formic acid, reflux
Ja,b=3.611/.,NOE>7%
B

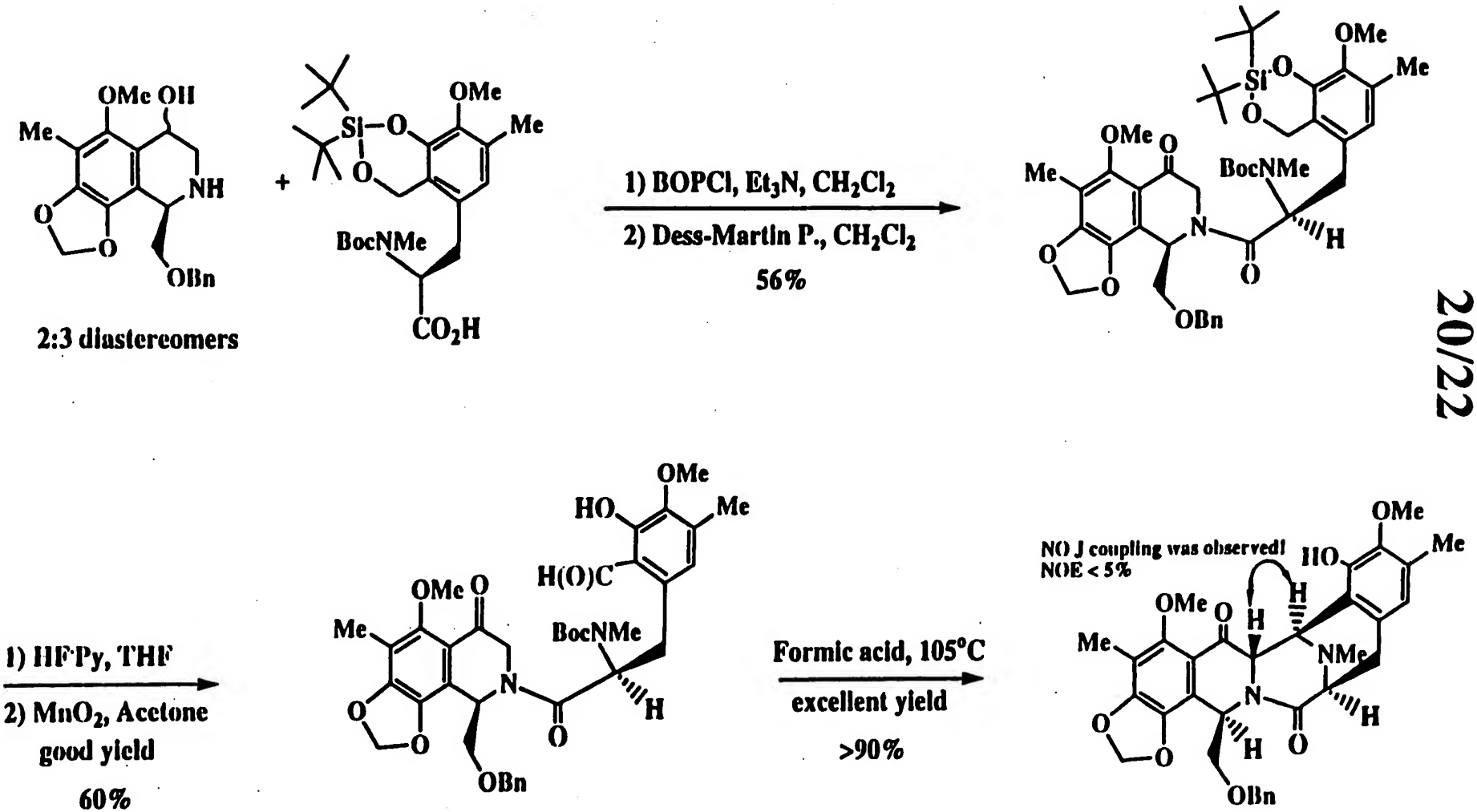
# FIGURE 11


OMe
MeO
Me
OMe
O
H
Me
NMe
OMe
N
MeO
H
O
OMe
OBn
AlH3, THF
good yield
OMe
MeO
Me
OMe OH
H
Me
NMe
OMe
N
MeO
H
OMe
OBn
1) Deoxygenation
2) Deprotection
OMe
MeO
Me
OMe
H
H
OM
Me
NMe
N
MeO
H
OMe
OH
1) BBr3, CH2Cl2*
2) 10N Nitric acid*
42%
OMe
O
Me
O
H
O
Me
NMe
N
MeO
H
O
NHCOCOMe
Saframycin B

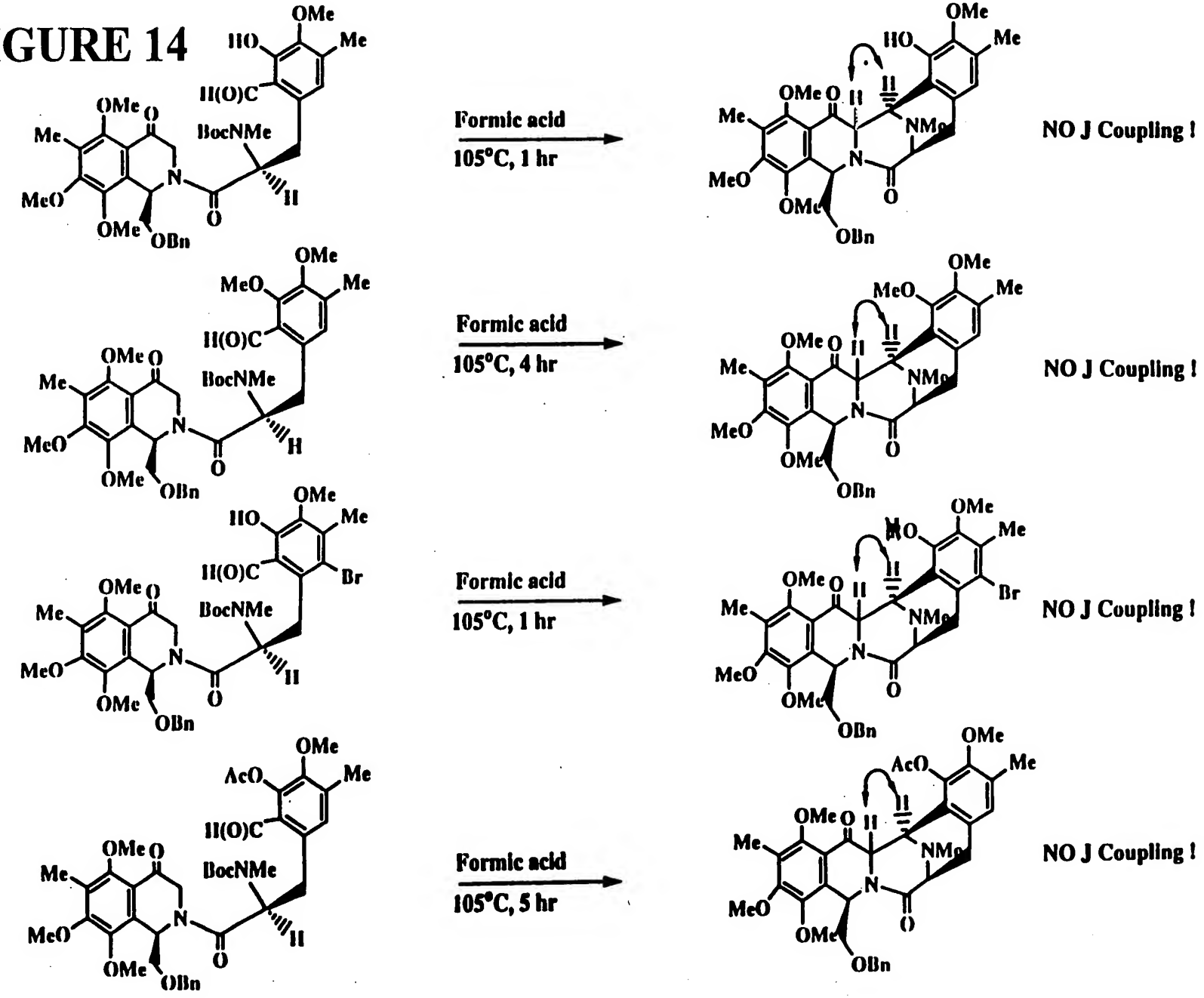
# FIGURE 12


1) MOMCl, i-Pr2NEt, CH2Cl2
2) Br OTBS ,K2CO3, CH3CN, reflux
3) PhNMe2, Toluene, 210°C
>60%
1) MeI,K2CO3,CH3CN
2) TBAF,THF
3) PivCl,Pyridine,CH2Cl2
91%
1) 3N HCl, THF-iPrOH
2) (CH2O)n,Et2AlCl,CH2Cl2
84%
1) t-Bu2Si(OTf)2,2,6-Lutidine,CHCl3
2) DIBAL-H,CH2Cl2,-78°C
89%
1) SAE, 97%, >95% ee
2) Ti(OiPr)2(N3)2,Benzene,reflux
3) DMP, Acetone, p-TsOH
88%
1) (Boc)2O, H2, Pd/C, EtOAc
2) MeI, NaH, THF-DMF, reflux
3) 80% AcOH, then KMnO4, NaIO3, Na2CO3, Dioxane-H2O
94%

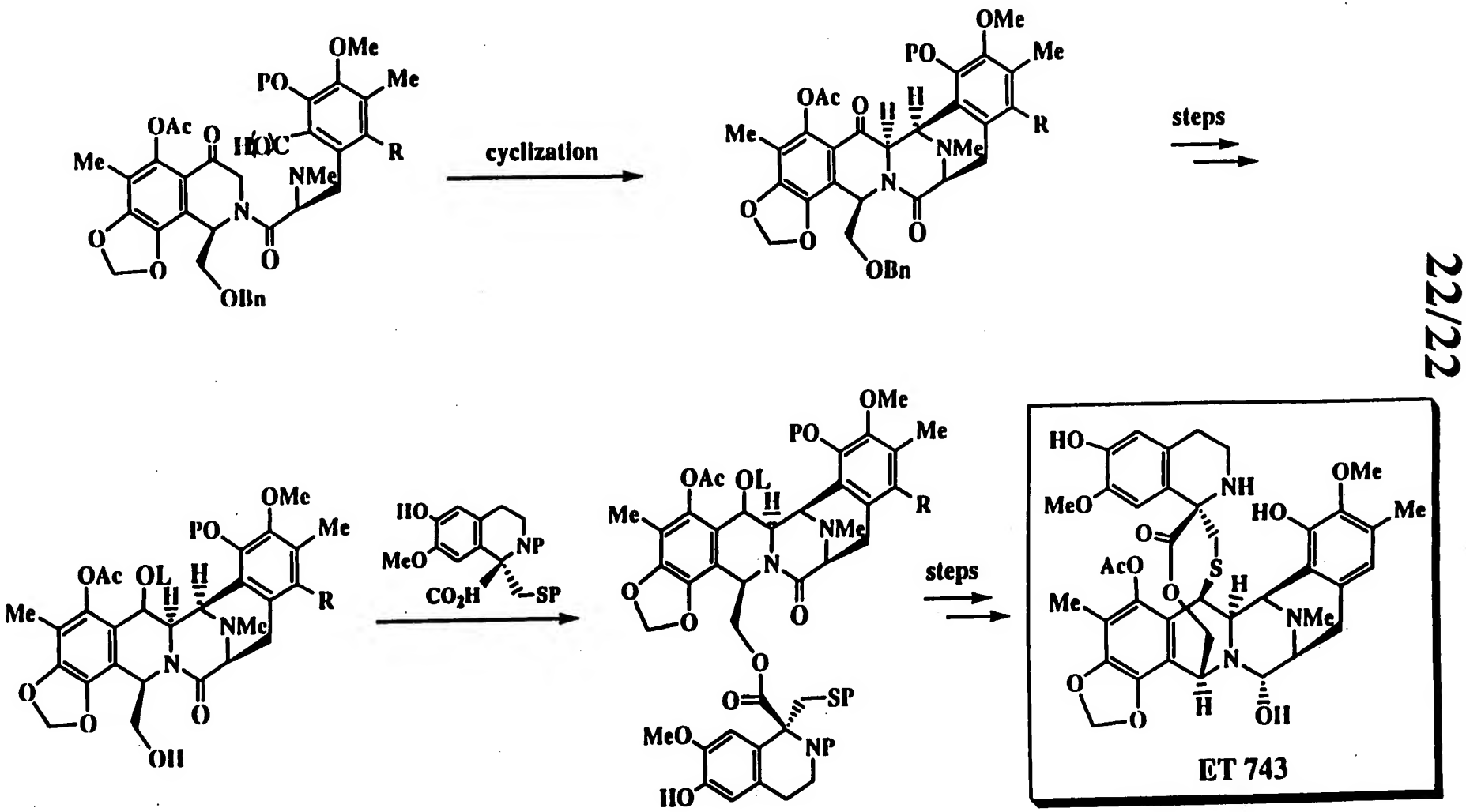
# FIGURE 13


OMe OH
Me
NH
O
O
OBn
2:3 diastereomers
+
Si
O
OMe
Me
BocNMe
CO2H
1) BOPCl, Et3N, CH2Cl2
2) Dess-Martin P., CH2Cl2
56%
OMe
Me
Si
O
O
OMe
O
Me
BocNMe
N
O
O
O
H
OBn
1) HF·Py, THF
2) MnO2, Acetone
good yield
60%
OMe
HO
Me
H(O)C
OMe
O
Me
BocNMe
N
O
O
O
H
OBn
Formic acid, 105°C
excellent yield
>90%
NO J coupling was observed!
NOE < 5%
OMe
HO
Me
OMe
O
H
H
Me
NMe
N
O
O
H
H
O
OBn

# FIGURE 14


Formic acid
105°C, 1 hr
NO J Coupling !
Formic acid
105°C, 4 hr
NO J Coupling !
Formic acid
105°C, 1 hr
NO J Coupling !
Formic acid
105°C, 5 hr
NO J Coupling !

# FIGURE 15


OMe
PO
Me
OAc
O
HO2C
R
Me
NMe
N
O
O
O
OBn
cyclization
OMe
PO
Me
OAc
O
H
H
R
Me
NMe
N
O
O
O
OBn
steps
OMe
PO
Me
OAc
OL
H
R
Me
NMe
N
O
O
O
OH
HO
MeO
NP
CO2H
SP
OMe
PO
Me
OAc
OL
H
R
Me
NMe
N
O
O
O
O
O
SP
MeO
NP
HO
steps
HO
MeO
NH
OMe
HO
Me
O
AcO
O
S
H
Me
NMe
N
O
O
H
OH
ET 743